

Median cleft of upper lip and pedunculated skin masses associated with de novo reciprocal translocation 46,X,t(X;16)(q28;q11.2)

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Abstract

We describe a de novo apparently balanced reciprocal translocation, 46,X,t(X;16)(q28;q11.2), in a 13 year old girl with median cleft of the upper lip, pedunculated skin masses on the nasal septum, short stature, and mental retardation. Pai syndrome is characterised by median cleft of the upper lip, pedunculated skin mass(es) on the face, and midline lipoma(s) of the central nervous system. The cause of this syndrome is unknown, although autosomal dominant inheritance has been proposed. The translocation breakpoints in the present patient may be candidate regions for a gene responsible for median cleft of the upper lip and pedunculated skin mass(es) on the face, including Pai syndrome.

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Keywords: Pai syndrome; median cleft lip; pedunculated skin mass; reciprocal translocation

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Pai syndrome (MIM 155145) is a rare genetic disorder characterised by median cleft of the upper lip and pedunculated skin mass(es) on the face as obligatory criteria and has been detected in eight patients (six males and two females).¹⁻⁶ In addition, midline lipoma(s) of the central nervous system has been described as part of the syndrome in two male patients.^{7,8} Psychomotor development is not impaired. At present, the cause of this syndrome is unknown, although autosomal dominant inheritance has been suggested.⁸

Here we report a Japanese girl with median cleft of the upper lip and pedunculated skin masses on the nasal septum associated with a de novo reciprocal translocation, (46,X,t(X;16)(q28;q11.2)). The possibility that one of the chromosome breakpoints is the critical region for median cleft of the upper lip and pedunculated skin mass(es) on the face including Pai syndrome is discussed.

Case report

The proband was the third child of a 31 year old G5, P2, A2 mother and a non-consanguineous 33 year old father. The first and third pregnancies resulted in healthy females. The second and fourth pregnancies ended in early spontaneous and induced abortions, respectively. The proband was born at 39 weeks of gestation after an uneventful preg-

nancy, labour, and delivery except for polyhydramnios. Apgar score was 9 at one minute. Birth weight was 3600 g, length 51.0 cm, and occipitofrontal circumference (OFC) 32.5 cm. Frontal bossing, hypertelorism, epicanthus, upward slanting, short palpebral fissures, two pedunculated skin masses on both sides of the nasal septum, a skin tag on the nasal tip, a broad nose, median cleft of the upper lip, high arched palate, downturned corners of the mouth, large ears, left hypoplastic anthelix, and broad big toes were noted at birth (fig 1). Her muscle tone was decreased. She had a perimembranous ventricular septal defect and ophthalmological abnormalities, including persistent pupillary membranes, left corneal leucoma, left microcornea, and heterochromia of the iris. She was tube fed because of poor sucking for two months. At 2 months of age, the cleft lip was repaired and the skin masses were excised. Histological examination showed the masses to be covered with normal skin tissue and to have a core of adipose tissue and striated muscle bundles. No cartilage was included in the tissue samples. She raised her head at the age of 8 months and was able to sit up unaided at 14 months. She could walk without support at 3 years 2 months of age and understood simple orders at 5 years. At 13 years of age she spoke no meaningful words but expressed herself by sign language. Her height was 138.3 cm (-2.8 SD), weight 31.1 kg (-2.0 SD), and OFC 51.0 cm (-1.7 SD).

At 2 years of age, computed tomography of the head showed mild dilatation of the anterior horn of the lateral ventricles without overt lipoma of the corpus callosum. Developmental quotient was 29. Dermatoglyphics were abnormal and included low total finger ridge counts (TFRC: 76), distal axial triradii (t'), additional digital triradii d', and fibular arch hallucal pattern on the left foot. The findings on intravenous pyelography and systemic skeletal survey were unremarkable. Thyroid function, serum chemistry, immunoglobulins, complete blood count, and urine were normal.

CYTOGENETIC FINDINGS

Chromosome analysis was made from peripheral lymphocyte cultures with PHA stimulation. The karyotype of the proband determined by high resolution GTG banding was 46,X,t(X;16)(q28;q11.2) (fig 2). Because of the very terminal breakpoint on Xq, fluorescence in situ hybridisation was performed using the whole chromosome paint X probe

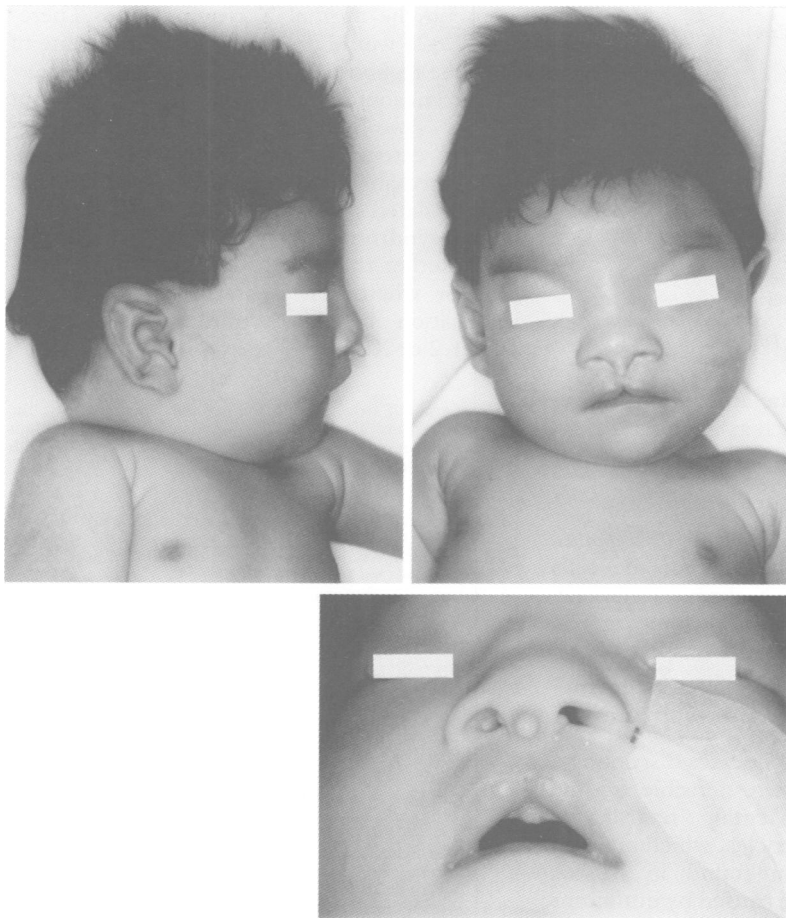


Figure 1 Front and lateral views of the proband aged 2 months (top). Close up view of the nose and the upper lip (bottom).

(Oncor) and showed a subtle translocation of the Xq terminal segment onto the derivative chromosome 16.

In X replication studies on the lymphocytes using the RBG technique, the derivative X chromosome was constantly late replicating in all 30 cells examined. In the majority of those cells with a late replicating derivative X chromosome, there was no evidence that inactivation had spread into the adjacent autosomal segment. Nevertheless, in two cells, the entire

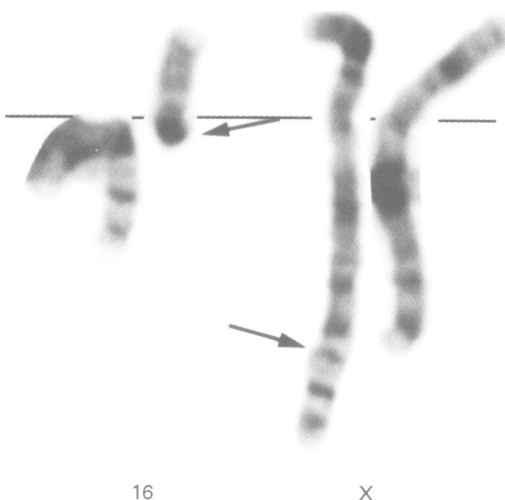


Figure 2 Partial G banded karyotype of the proband. Arrows show the breakpoints at 16q11.2 and Xq28 on the translocated chromosomes.

translocated portion of chromosome 16 had a later replication time than the normal homologue. The remaining part of the terminal Xq segment attached to the derivative 16 chromosome was so tiny that the replication pattern could not be elucidated (fig 3). Both parents had a normal chromosome constitution. An EBV transformed lymphoblastoid cell line from this patient (KCMC-448) is available from Dr M Masuno.

Discussion

CORRELATION OF CLINICAL MANIFESTATIONS WITH CYTOGENETIC FINDINGS

The cause and gene locus responsible for median cleft of the upper lip and pedunculated skin mass(es) on the face in Pai syndrome are unknown. Autosomal dominant inheritance has been proposed in a family in which the father of a male patient with Pai syndrome showed coloboma of the right iris and some facial dysmorphism.⁸ However, coloboma of the iris has not been observed in previously reported patients with Pai syndrome and may not be part of the syndrome. The mother of the male patient described by Pai *et al*⁷ had enlarged lateral ventricles and a similar facial appearance to her son. As the incidence of Pai syndrome is much higher in males than in females, X linked recessive inheritance could not be excluded.

Several possible causal relations of clinical manifestations and a balanced X;16 translocation in the present patient follow.

Functional monosomy of 16q

Inactivation is apparently restricted to the X chromosomal segment of the derivative X chromosome in the majority of the lymphocytes, while a small percentage of them showed spreading of inactivation from the derivative X chromosome to the entire translocated portion of chromosome 16. However, our observation is only a finding of cytogenetic resolution, and tissue differences in spreading of inactivation or instability of inactivation of an autosomal segment translocated to the X chromosome (reactivation) should also be considered. Thus, most of the clinical manifestations in the present patient may be the result of (partial) functional 16q monosomy. Some clinical features, including postnatal growth retardation, mental retardation, and dysmorphism such as frontal bossing, hypertelorism, upward slanting, short palpebral fissures, high arched palate, and broad big toes, resembled those of partial 16q monosomy.⁹ Several genes have been mapped on the long arm of chromosome 16. Guanine nucleotide binding protein (GNAO1, MIM 139311), which is a signal transducing molecule assigned to 16q13 and E-cadherin (CDH1, MIM 192090) as a morphogenetic regulator at 16q22.1, may be candidate genes for Pai syndrome.

Functional disomy of terminal Xq segment

As the terminal Xq portion, lacking the X inactivation centre (XIST), translocated onto the derivative 16 chromosome may never be inactivated, functional disomy of the terminal

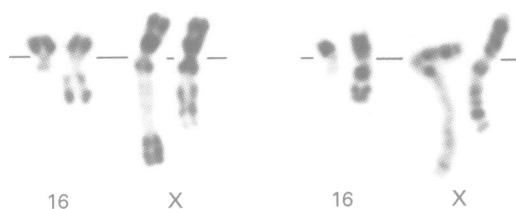


Figure 3 RBG replication banding. Derivative X chromosome is constantly late replicating. In the majority of the peripheral lymphocytes, inactivation is apparently restricted to the X chromosomal segment (left). In a few cells the late replication of the derivative X chromosome extends to the entire translocated 16q segment (right).

Xq segment may in part be attributable to the clinical manifestations, such as mental retardation, of the present patient, as described by Sart *et al.*¹⁰

Direct interruption of a gene(s) at the breakpoints

The strong selective advantage for the cells with an inactive derivative X chromosome may be the result of disruption of an important X linked gene(s) at Xq28. As the proportions of cells with an inactivated derivative X chromosome may be different among tissues,¹¹ some active derivative X chromosomes in tissues other than peripheral lymphocytes disrupting a gene(s) at Xq28 may be responsible for the clinical symptoms. Mental retardation, aphagia, and dilated ventricles, which are part of the clinical spectrum found in MASA syndrome (MIM 303350) caused by mutations of the L1CAM gene located on Xq28,¹² were present, but not torticollis, asymmetrical face, keloids, or renal dysplasia (MIM 314300), which are seen in patients with balanced translocations between Xq28 and autosomes.^{10 13-15}

Another breakpoint at 16q11.2 which consists of heterochromatin is unlikely to correlate with the abnormal phenotypes.

Unmasking of a mutation on the "normal" X chromosome by rearrangement induced non-random inactivation of the derivative X chromosome

If the normal X chromosome contains a mutated locus, non-random X inactivation of the derivative X chromosome may incidentally lead to the clinically affected status of the present patient, as described by Nisen *et al.*¹⁶ If so, the unmasking of a mutation could be at any

locus on the normal X chromosome. Therefore, Xq28 would not necessarily be the site of the gene responsible for this syndrome.

Chromosome analysis has been carried out on only two patients with Pai syndrome.^{7 8} Careful cytogenetic studies in other patients with median cleft of the upper lip and pedunculated skin mass(es) on the face including Pai syndrome would be of interest to establish whether the present association is fortuitous or whether it is an indication for the localisation of this syndrome at or near 16q11.2 or Xq28.

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- Sharma LK. Median cleft of the upper lip. *Plast Reconstr Surg* 1974;53:155-7.
- Ponniah RD. Midline cleft lip with associated abnormalities. *J Laryngol Otol* 1977;91:177-81.
- Nakamura J, Tomonari H, Goto S. True median cleft of the upper lip associated with three pedunculated club-shaped skin masses. *Plast Reconstr Surg* 1985;75:727-31.
- Scrimshaw GC. Previous reports on median cleft lip. *Plast Reconstr Surg* 1986;77:159-60.
- Lewin ML. Median cleft lip with pedunculated skin masses. *Plast Reconstr Surg* 1987;79:843-4.
- Reardon W, Jones B, Baraitser M. Median clefting of the upper lip associated with cutaneous polyps. *J Med Genet* 1990;27:337-8.
- Pai GS, Levkoff AH, Leithiser RE. Median cleft of the upper lip associated with lipomas of the central nervous system and cutaneous polyps. *Am J Med Genet* 1987;26:921-4.
- Rudnik-Schöneborn S, Zerres K. A further patient with Pai syndrome with autosomal dominant inheritance? *J Med Genet* 1994;31:497-8.
- Callen DF, Eyre H, Lane S, *et al.* High resolution mapping of interstitial long arm deletions of chromosome 16: relationship to phenotype. *J Med Genet* 1993;30:828-32.
- Sart DD, Kalitsis P, Schmidt M. Noninactivation of a portion of Xq28 in a balanced X-autosome translocation. *Am J Med Genet* 1992;42:156-60.
- Schmidt M, Sart DD. Functional disomies of the X chromosome influence the cell selection and hence the X inactivation pattern in females with balanced X-autosome translocations: a review of 122 cases. *Am J Med Genet* 1992;42:161-9.
- Jouet M, Rosenthal A, Armstrong G, *et al.* X-linked spastic paraplegia (SPG1), MASA syndrome and X-linked hydrocephalus result from mutations in the L1 gene. *Nat Genet* 1994;7:402-7.
- Sands ME. Mental retardation in association with a balanced X-autosome translocation and random inactivation of the X chromosomes. *Clin Genet* 1980;17:309-16.
- Hellkuhl B, de la Chapelle A, Grzeschik KH. Different patterns of X chromosome inactivity in lymphocytes and fibroblasts of a human balanced X;autosome translocation. *Hum Genet* 1982;60:126-9.
- Zuffardi O, Fraccaro M. Gene mapping and serendipity. The locus for torticollis, keloids, cryptorchidism and renal dysplasia (31430, McKusick) is at Xq28, distal to the G6PD locus. *Hum Genet* 1982;62:280-1.
- Nisen P, Stamberg J, Ehrenpreis R, *et al.* The molecular basis of severe hemophilia B in a girl. *N Engl J Med* 1986;315:1139-42.